REMARKS

Claims 1-26 have been amended. Claims 27-32 have been added. Subsequent to the entry of the present amendment, claims 1-32 are pending. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

I. Amendments to the Claims

Claims 1-26 have been amended to clarify that the claims are directed to series of polynucleotides, oligonucleotides and/or primers. Support for these amendments can be found throughout the specification, particularly at page 32, [0103] to p. 33, [0106]. As such, these amendments add no new matter.

In addition, claims 1-26 have been amended as to form to emphasis that the series of recited polynucleotides, oligonucleotides and/or primers are Markush groups.

II. Restriction Requirement

In the Office Communication mailed June 14, 2006, the Examiner has required restriction to "ONE particular single nucleotide polymorphism for examination." Office Communication at p. 2. In addition, the Examiner has required a further election of "a specific probe sequence and a single pair of primers associated with the elected single nucleotide polymorphism." *Id.*

In order to be fully responsive to the restriction requirement, Applicants provisionally elect the single nucleotide polymorphism of marker MMT07944 as set forth in SEQ ID NO:20614, with traverse. Applicants further elect 1) the extension primer set forth in SEQ ID NO:23124 and 2) the single pair of primers wherein each primer has the sequence of nucleotides 275-350 of SEQ ID NO: 20614, except that for the nucleotide corresponding to position 300 of SEQ ID NO: 20614, which is indicated in the sequence listing as "r" meaning that it can be a "g" or an "a" (see 37 CFR §1.821; WIPO Standard ST.25 (1998), Appendix 2, Table 1), for the first primer, the terminal nucleotide in this position is a "g" and for the second primer, the terminal nucleotide in this position is an "a."

Traversal

In the Office Communication, the Restriction Requirement to "ONE particular single nucleotide polymorphism[,].... a specific probe sequence and a single pair of primers associated with the elected single nucleotide polymorphism" was allegedly justified by the argument that "[n]ucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141." Office Communication at 2.

The Examiner further stated that "[t]he search and examination of all possible groups would pose an enormous burden on the examiner and on the PTO search resources. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter." *Id.*

However, the restriction rules for polynucleotide sequences limit the number of sequences that can be examined largely on the basis of search burden. While this is an important consideration, it is well established that search burden alone is insufficient grounds for restriction.

In addition, the "inventions" sought to be restricted must be shown to be **independent** or **distinct** ***as claimed.*** Thus, the basic requirement for a proper Restriction requirement is two-fold. *See* MPEP 803.I. First, the alleged inventions must be independent or distinct as claimed. *Id.* Second, there must be a serious burden on the Examiner if restriction is not required. *Id.* Nevertheless, the courts and Patent Office have also recognized "an applicant's right to define what he regards as his invention as he chooses." *See, e.g., In re Harnisch*, 206 U.S.P.Q. 300, 305 (CCPA 1980).

The Patent Office has determined that nucleic acid sequences "***that encode different proteins*** are structurally distinct chemical compounds." MPEP 803.04. This determination forms the basis for presuming that each polynucleotide sequence recited in a claim is an independent and distinct invention. Applicants do not dispute this presumption as it applies to nucleic acid sequences that have been shown to encode a protein. However, it is well known that the vast majority of a mammalian genome is comprised of non-coding regions. Within the genome, there are sequences, commonly referred to as "markers," that simply provide a reference point on a chromosome.[1] Markers can, but need not be, located in a nucleic acid sequence that encodes a protein. *See* specification at 28, [0072]. Moreover, their function as a ***marker*** is not dependent on, and is typically separate from, whether the sequence resides in a protein-encoding sequence or not. Indeed, their function is to ***locate*** sequences that encode proteins and to facilitate the ***association of genes*** with phenotypic traits, which may be complex and involve many encoded proteins and genes. If the relationship between a particular sequence that encodes a protein and the phenotypic trait were known, there would be no need for markers.

Single nucleotide polymorphisms are markers for a particular location on the chromosome that can be used to identify genes and correlate traits. As a group, they have no known protein-encoding function. They simply represent a difference that is observed at a single nucleotide position on a chromosome. In virtually all instances, there are only two forms of the SNP. Because of this difference, molecular geneticists can map traits to certain regions of a

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[1] The definition of a "marker" is: "An identifiable physical location on a chromosome (for example, restriction enzyme cutting site, gene) whose inheritance can be monitored. Markers can be expressed regions of DNA (genes) or some segment of DNA with no known coding function but whose pattern of inheritance can be determined." *See* http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=marker&action=Search+OMD, a copy of which is attached hereto as Exhibit A.

Merriam-Webster's online Medical dictionary provides the following definition of "marker": "something that serves to identify, predict, or characterize." *See* http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=marker, a copy of which is attached hereto as Exhibit B.

The same dictionary further specifies that at genetic marker is
"a readily recognizable genetic trait, gene, DNA segment, or gene product used for identification purposes especially when closely linked to a trait or to genetic material that is difficult to identify -- called also marker" *See* http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=genetic+marker, a copy of which is attached hereto as Exhibit C.

chromosome by association with one variety of the SNP or another, and thereafter, use the association information to predict whether an animal [or human] will have the trait.

The significance of SNPs is ***not*** related to whether one SNP is present in a nucleic acid sequence that encodes a particular protein and a different SNP is present in a nucleic acid sequence that ***encodes a different protein***. Indeed, if the causative relationship between a SNP and the difference in proteins that leads to a phenotypic trait were clearly understood, it would not be necessary to use SNPs as markers. One could go straight to the known causative differences between proteins or the nucleic acid sequences that encode them to infer a phenotypic trait. Indeed, in quantitative genetic approaches using SNPs, the genes and "genetic architecture of the trait itself is treated as a black box, with no knowledge of the number of genes that affect the trait, let alone of the effects of each gene or their locations in the genome." *See e.g.,* Dekkers & Hospital, Nature Rev. Genetics 3:22-32, 22 (2002), a copy of which is attached hereto as Exhibit D. This type of analysis is based on "Fisher's infinitesimal genetic mode, in which the trait is assumed to be determined by an infinite number of genes, each with a infinitesimally small effect [on the trait]." *Id.*

Accordingly, applicants submit that the fundamental assumptions under which the Patent Office has made a presumptive determination that each nucleic acid sequence is an independent and distinct invention do not apply to SNPs, particularly the SNPs claimed in claims 1-26 (as amended) and new claims 28-32.

As discussed above, SNPs functioning as markers identify a particular position on a chromosome – a point of reference. Unfortunately, the nature of the genome combined with Patent Office rules do not allow this single point of reference to be expressed in the absence of the surrounding sequence information. A SNP, as recited in claims 1-26 (as amended) and new claims 27-32, is in fact a single point – not a gene or a protein-encoding nucleic acid. However, the limitations of the art of molecular biology requires that a sufficient amount of nucleic acid sequence information flanking that single point is recited in order to uniquely identify the single

point. Furthermore, the Patent Office requires that nucleic acid sequences be expressed by SEQ ID NOs, as described in MPEP 2421-2425.

Nevertheless, the essential information represented by a SNP as recited in claims 1-26 (as amended) and new claims 28-32 is simply a single nucleotide polymorphism which identifies or marks a single point on a chromosome.

Applicants submit that the SNPs recited in claims 1-26 (as amended) and new claims 27-32 are not independent and distinct as claimed and respectfully request reconsideration and withdrawal of the restriction requirement.

The SNPS of the Present Invention are Not Independent

According to the MPEP, "[i]nventions as claimed are independent if there is no disclosed relationship between the inventions, that is, they are unconnected in design, operation, and effect." MPEP 806.06. Applicants submit that the SNPs as recited in claims 1-26 (as amended) and new claims 27-32 are intimately connected in design, operation and effect.

As points of reference on a chromosome, SNPs permit the ability to associate a region or position of the chromosome with a trait of interest. Such mapping requires a multitude of SNPs at various positions on the chromosome. *See e.g.*, specification at p. 8. [0021]. Locating a trait of interest having an unknown location would not be possible if only a single point of reference were available in the genome. *Id.* The skilled artisan requires multiple points along each of the chromosomes of an animal in order to locate a gene. *See e.g.*, specification at Example 2, p. 60.

However, given a large pool of SNPs or reference points, no individual points is *a priori* more effective than another for locating a gene or genes contributing to a trait. Furthermore, SNPs that are sufficiently close to each other are essentially interchangeable because they mark the same approximate location on the chromosome. *See* specification at p. 13, [0035].

Once a group of SNPs has been associated with an individual trait, groups of SNPs are similarly connected in design, operation, and effect. Furthermore, the skilled artisan will appreciate that use of only one, individual SNP to infer a trait is limited. *See, e.g.*, Andersson &

Georges, *Nature Rev. Genetics*, 5:202-212 (2004), a copy of which is attached hereto as Exhibit E. For example, in order to be able to track meat of a bovine subject, a series of SNPs is required. *See* Specification at p. 32, [0103] to p. 33, [0106]. Although a inference can be made using a single SNP associated with the trait, unless that SNP identifies a causative mutation in a gene responsible for determining the trait, the inference that can be made is often only partially predictive. Thus a strong inference typically requires the identification of multiple SNPs. *See* specification at p. 19, [0058].

At the same time, however, any two SNPs associated with a trait may be functionally interchangeable or identical for the purpose of making an inference. SNPs that are located in close proximity to each other can be essentially interchangeable in ability to infer a trait by association. Furthermore, the actual number of SNPs that must be used to infer a trait is not fixed, but rather relates to the degree or strength of the inference that can be made; the more SNPs or points that are used to make the inference, the greater the statistical significance of that inference. Specification at p. 19, [0058].

The SNPS of the Present Invention are Not Distinct

Similarly, Applicants submit that the SNPs as recited in claims 1-26 (as amended) and new claims 27-32 are not distinct inventions as claimed. The test for distinct inventions, as set forth in the MPEP, is:

> inventions are distinct if
>
> (A) the inventions as claimed do not overlap in scope, i.e., are mutually exclusive;
>
> (B) the inventions as claimed are not obvious variants; and
>
> (C) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect.

See MPEP 806.05(c).

Applicants submit that the SNPs as recited in claims 1-26 (as amended) and new claims 27-32 fail to meet at least elements (A) and (C) of the test for distinctness, and therefore are not

distinct inventions. Regarding element (A) the SNPs of the claimed invention overlap in scope. As discussed above, any two closely spaced SNPs can be interchanged with respect to mapping. Simply put, one point is a good as another, provided enough points are available. When the use of the SNP is for a particular trait inference, the more SNPs associated with the trait, the better. Yet within a group of SNPs that are informative or associated with a trait, particular subsets or individual SNPs may not be superior to others. Indeed, either of two or more closely linked SNPs can be used to infer a trait, yet the inference will be stronger if a third or fourth or fifth SNP is also determined. Specification at p. 19, [0058]. Furthermore, when a trait is polygenic and/or when epistasis is involved it the phenotypic expression of the trait, multiple SNPs are absolutely required to make an appropriate inference. Specification at p. 34, [0113] to p. 35, [0115]. Thus, Applicants submit that the SNPs recited in claims 1-26 (as amended) and new claims 27-32 are not mutually exclusive and therefore fail to meet element (A) of the test for distinct inventions.

Regarding element (C) of the test for distinctness, the SNPs of claims 1-26 (as amended) and new claims 27-32 are not only capable of use together, they ***must*** be used together for trait mapping and in most applications of trait inference. In addition, the SNPs of claims 1-26 (as amended) and new claims 27-32 share the same design, operation, function and effect – they simply represent points on the chromosome and although each SNP represents a specific point, in the context of their role as claimed, each functions to facilitate gene mapping and trait inference by marking that particular point to the same effect as any other SNP. Thus, Applicants submit that the SNPs as recited in claims 1-26 (as amended) and new claims 27-32 fail to meet element (C) of the test for distinct inventions, and therefore are not distinct. *See also,* MPEP 806 (C) ("Where inventions are related as disclosed but are not distinct as claimed, restriction is never proper.").

Taken together, Applicants submit that the SNPs as recited in claims 1-26 (as amended) and new claims 27-32 are neither distinct nor independent. Accordingly, restriction to a single SNP is improper under MPEP 803 (stating that "[u]nder the statute, the claims of an application

may properly be required to be restricted ... only if they are ...and they are either independent or distinct.")(citations omitted).

Accordingly, Applicants respectfully request reconsideration and withdrawal of the Restriction Requirement.

Applicants are Entitled to Claim a Reasonable Number of at Least Ten (10) Sequences

Notwithstanding Applicants' submissions above supporting the lack of independence of distinctiveness of the claimed sequences, the Director "has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application." Specifically, the MPEP states that "ten sequences constitute a reasonable number for examination purposes...[that] will be examined in a single application without restriction."

Applicants submit that claims 1-26 (as amended) and new claims 27-32, which recite 10 sequences, constitute a reasonable number of sequences for examination purpose according to the MPEP.

Accordingly, reconsideration and withdrawal of the restriction requirement is respectfully requested.

The Restriction Requirement as Applied to the Recited Markush Groups is Improper.

According to the MPEP, "members of [a] Markush group ... ordinarily must belong to a recognized physical or chemical class or to an art-recognized class." MPEP 803.02. When such a Markush group is present, it is improper to restrict individual members of the group. *Id.*

Moreover, the MPEP has a separate subsection that deals particularly with "Markush-type generic claims which recite a plurality of alternatively usable substances or members." *Id.* According to the MPEP, this section applies to the type of claims that contain "a recitation by enumeration...because there is no appropriate or true generic language," that can substitute for the recitation. *Id.* These Markush-type claims "***may include independent and distinct***

inventions" including claims where "two or more of the members [of the Markush group] are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s)." *Id.* (emphasis added).

The procedure for these types of claims does not include immediate, outright restriction of the Markush group to individual members. Instead, the Examiner is directed that

> [i]f the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions.

Id.

In the event that the examination of the members of a Markush group is considered to be a serious burden, then the Examiner is permitted to "require a ***provisional*** election of a single species prior to examination on the merits." *Id.* (emphasis added). "Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability." Only after examination and a finding that the "Markush-type claim is not allowable over the prior art," can the restriction be applied with respect to the elected species. Upon such a finding, "the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration." *Id.*

Applicants submit that to the extent that the single-nucleotide polymorphisms, probe sequences, and pair of primers recited in Markush form in claims 1-32 are held to be independent and distinct inventions, the outright restriction of each member of the Markush group is improper.

Applicants submit that the proper procedure in this case is to first determine whether the entire group can be examined without undue burden, and to do so where possible. If this is not

possible, then the proper procedure is to require a ***provisional*** election of one species of the genus by enumeration of claim 1-32 for examination on the merits, subject to continued examination of a reasonable number of species upon finding the elected species patentable.

Accordingly, Applicant respectfully request that if the restriction requirement is not withdrawn *in toto*, then the elections made by the present response are treated as an election of species for initial search and examination and that the once the claims reading on the elected species are found patentable, the search and examination is continued for a reasonable number of species.

Check number 583884 in the amount of $1590.00 is enclosed for the requisite Four-Month Extension of Time fee. No other fee is deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees that are required, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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